Cardio DIGEST
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Editorial

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New-onset diabetes and statin therapy

Over the past few years there has been considerable interest in the possibility of an increased incidence of new-onset diabetes with statin use. Before considering the available clinical evidence and its implications, one needs to consider the plausibility of such an association.

A number of *in vitro* and *in vivo* studies have demonstrated that (mainly lipophilic) statins may be associated with a deterioration in glucose control. Studies have revealed atorvastatin to decrease adipocyte glucose uptake (Takaguri et al, 2008), and is associated with an increase in HbA_{1c} level in people with hypercholesterolaemia (Ishikawa et al, 2006a). Simvastatin has also been demonstrated to decrease insulin sensitivity in small short-term studies (Koh et al, 2009). Both atorvastatin and simvastatin decrease insulin secretion in beta-cells (Ishikawa et al, 2006b). These changes observed with atorvastatin and simvastatin have not been replicated for pravastatin. In contrast, no differences have been observed for rosuvastatin with atorvastatin in people with metabolic syndrome in terms of insulin sensitivity (Stalenhoef et al, 2005).

A recent analysis of a large cohort of the Veteran's Affairs Health Care System demonstrated that statins produced mild increases in glycaemia over a 2-year period in people without diabetes as well as in those with diabetes (Sukhija et al, 2009). In people with elevated levels of high-sensitivity C-reactive protein, rosuvastatin treatment was associated with mild, but significant, increases in the identification of incident diabetes (Ridker et al, 2008). By clear contrast, the West of Scotland Coronary Prevention Study (WOSCOPS) suggested a 30% reduction in developing diabetes with the use of pravastatin (Freeman et al, 2001). A recent meta-analysis of six randomised controlled trials with a large number of study participants did not demonstrate an increase in incident diabetes with statin use (relative risk 1.06) (Rajpathak et al, 2009). However, if the data from the WOSCOPS study were excluded (on grounds of use of pravastatin), the risk of new development of diabetes increased by a small amount (relative risk 1.13). The exclusion of WOSCOPS was based on *in vivo* and *in vitro* findings of differences in statins and their effects on insulin resistance and glycaemic parameters (Rajpathak et al, 2009). However, further levels of heterogeneity are also introduced in such trials, based on diagnosis of diabetes, duration of follow-up, study group composition (such as inclusion of male and female subjects) and baseline BMI values.

Regardless of the data, where does the practising clinician stand at present? Would an increase in glycaemic parameters or, indeed, incident diabetes reduce the use of statins in individuals at high-risk of cardiovascular (CV) disease, such as those with diabetes? It is, of course, well recognised that people at increased CV risk, with or without diabetes, accrue considerable reductions in CV events and overall mortality with the use of statins. Indeed, the risk reduction may be the greatest in subjects with the highest risk. Given the improvement of CV risk observed with this treatment, the small increase in incident diabetes may not off-set the clear benefits. As CV disease accounts for the large proportion of deaths in people with diabetes, the protective effect of statins on this key complication would support the continual usage of these agents, regardless of a small possible increase in incident diabetes, which remains as yet to be confirmed. Thus, in the absence of new data, there should be no significant change in our clinical practice at present.

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